Systematic Reviews on Early Postnatal EFA/LCPUFA Intake and Visual Resolution Acuity in Healthy Infants

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SPECIFIC AIMS

The purpose of this presentation was to discuss the conceptualization, methods, and results of two systematic reviews on the relationship of long-chain polyunsaturated fatty acid (LCPUFA) intake and visual resolution acuity in healthy infants. The purposes of the original project were to: (1) advance knowledge on postnatal essential fatty acid (EFA)/LCPUFA intake as factors regulating visual system development, (2) derive combined estimates of visual resolution thresholds based upon information from studies of early postnatal dietary EFA/LCPUFA intake and visual resolution acuity in infancy, and (3) derive sample size estimates from combined estimates for the use in planning future clinical trials.

For more detail you may accessed our work electronically *via* websites for the American Academy of Pediatrics (http://www.pediatrics.org/) and Elsevier Science (http://www.sciencedirect.com). The citations are:

PEDIATRICS Vol. 105 No. 6 June 2000, pp. 1292-1298
Meta-analysis of Dietary Essential Fatty Acids and Long-Chain Polyunsaturated Fatty Acids as They Relate to Visual Resolution Acuity in Healthy Preterm Infants. John Paul SanGiovanni, DSc, Socorro Parra-Cabrera, MPH, Graham A. Colditz, MD, DPH, Catherine S. Berkey,DSc, and Johanna T. Dwyer, DSc. http://www.pediatrics.org/cgi/content/full/105/6/1292

Early Human Development Vol. 57, Issue 3, March 2000, pp. 165-188
Dietary essential fatty acids, long-chain polyunsaturated fatty acids, and visual resolution acuity in healthy fullterm infants: a systematic review. John Paul SanGiovanni, Catherine S. Berkey, Johanna T. Dwyer, and Graham A. Colditz.

CONTENT OF PRESENTATION

Background and Significance. Intake of LCPUFAs represented our conceptual exposure of interest. In planning the analyses we were most interested in docosahexaenoic acid (DHA, 22:6ω-3) and the balance and composition of total LCPUFAs, since these nutrients may operate as *modifiable risk factors* in the prenatal, perinatal and early postnatal periods. During the first part of the presentation we discussed the public health significance of studying nutritional factors that are both not widely distributed in the food supply and differentially accreted/retained as structural components of retinal membranes. DHA is implicated to operate in a number of credible biologic mechanisms modulating structural and functional aspects of visual sensation, perception, and development. I reviewed the evidence base supporting these concepts. The main points of the overview on LCPUFA Intake → Status ↔ Structure ↔ Function were:

- Retinal tissue status of DHA is modifiable by and dependent upon dietary intake.
- DHA is selectively accreted and retained in photoreceptor outer-segments.
- Outer segment disc membranes are highly concentrated with DHA.
- Humans with metabolic ω-3 LCPUFA deficiencies exhibit visual deficits that respond to supplementation.
- Humans with inherited retinal degenerations have low circulating levels of DHA.
- The structural nature of LCPUFAs alters biophysical properties of membranes in model systems.
- ω-3 LCPUFAs may modify factors and processes controlling gene expression, cellular differentiation and survival.

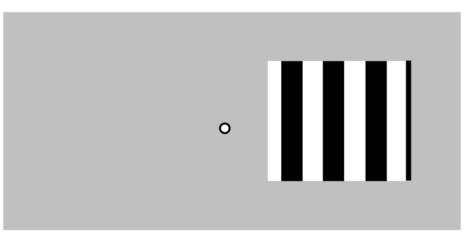
Research Question. Our research question was: Do healthy preterm/fullterm infants consuming a source of ω-3 LCPUFAs early in infancy perform better on acuity tests than those consuming an ω-3 LCPUFA-free diet?

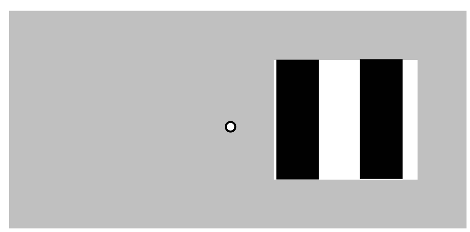
While this general question was constrained by the nature[1] of extant studies, we felt strongly that it was informative in developing combined estimates of performance differences. A number of factors prevented us from conducting meta-regression of LCPUFA intake levels on acuity. Some of these factors were technical (e.g. the number of data points required to derive stable parameter estimates). Others were conceptual (e.g. the dynamics of accretion and levels necessary for human retinal tissue sufficiency was not well understood at the time of publication); while random allocation of treatment should have equated study groups on these factors, there was no feasible way to ascertain the degree their variation for purposes of our analyses.

Outcome. The conceptual outcome was visual resolution acuity. Visual representation of pattern information is a fundamental perceptual function necessary for recognition, identification, and determination of the physical properties of objects. The effectiveness of pattern vision is dependent upon the accuracy with which the observer detects and encodes the spatial distribution of intensity or wavelength differences that define surfaces in the physical world. Visual resolution acuity is the threshold or maximum resolving capacity of the visual system.

Our analytic outcome variable was the difference in acuity between infant groups consuming an LCPUFA-supplemented diet and those consuming an LCPUFA-free diet. We derived combined estimates of acuity differences by age categories. Outcomes were expressed in octaves ($\log_2$) of cycles per degree of visual angle. A one octave difference is a doubling or halving of the number of cy/deg (a unit of spatial frequency) resolved. Spatial frequency is the number of pattern repetitions per degree of visual angle. Acuity was reported in cycles per degree (Cy/deg) of visual angle and was calculated and plotted on an octave scale.[i] The **Figure** displays square-wave gratings with elements containing elements with a 1 octave difference in spatial frequency. It was necessary to use a difference score (v. absolute acuity threshold) in order to account for inter-individual and -laboratory differences in testing technique.

Figure. Acuity cards with a 1-octave difference in spatial frequency.





Search Strategy, Study Selection & Data Extraction. We searched for prospective studies on EFA/LCPUFA intake, visual acuity measurements in first year of life from the following data sources: bio-medical reference databases (MEDLINE & Health STAR), review article/chapter reference sections, monographs, and consultation with authors. Studies selected for review had adequate methodological information on study design and conduct. Data were extracted independently by 2 researchers.

Systematic Review. We organized and published results on study-, tester-, and subject-based qualities of extant studies that may vary independently with acuity performance, acuity measurement, LCPUFA intake, and LCPUFA metabolism.

[1] Tables 1 through 3 in *Pediatrics* and *Early Human Development* provide a summary of study-, tester-, and subject-based factors.

Study-based factors included:

- study design
- formation, surveillance, and follow-up of study groups
- appropriateness of comparison groups
- outcome measure, protocol, and measurement properties
- number of infants enrolled/completing protocol
- dietary composition and duration of intake
- time period in which study was conducted
- study site

Tester-based factors included: number, experience, and training. Subject-based factors included: maternal/infant demographics and estimated age of subjects.

Meta-Analysis. We used methods developed by Der Simonian & Laird to derive combined estimates of performance differences, estimate the magnitude of effect, and to test heterogeneity of the sample. A major issue in meta-analysis is modeling outcome variability. The Der Simonian & Laird method first applies and tests the assumptions of a fixed effects model. Fixed effects should be modeled when variability in outcome is exclusively due to random variation and a single underlying effect of treatment is operating. If these assumptions may not be applied with a reasonable degree of certainty then a random effects model is used. Assumptions in this case are: (1) variability in outcome is due to random variation and additional sources of variation in results between individual studies, and (2) a different underlying treatment effect is operating in each study.

Results. We presented results separately for preterm and fullterm infants mainly because infants born prior to the third trimester of gestation miss the major period of maternal-fetal LCPUFA accretion. Preterm infants are also at higher risk for pathology in visual systems structures. We presented results separately for behavioral and electrophysiological tests, since they tap different visual processes. **Table 1** displays results for behavioral tests. Confidence limits including values of different signs are not different on the basis of statistical testing (e.g. a value of zero represents no difference between groups). Positive values indicate that subjects consuming ω-3 LCPUFAs scored higher as group. Randomized comparisons provided the greatest strength of inference and we used these results to guide our inferences.

For the preterm group, differences were observed at 2 and 4 months. The magnitude of the difference was approximately 0.5 octaves at 2 months. In other words, the group consuming formula with ω-3 LCPUFAs were able to resolve stimulus elements that were 30% thinner than the maximum resolvable stimulus width for the ω-3 LCPUFA-free group. For the fullterm group differences were observed at 2 months.

Table 1. Combined Estimates of Acuity Differences in Healthy Infants Measured With Behavioral Methods.

	Preterm Infants		Fullterm Infants	
Age Months	Comparisons	Combined Difference (95%CI)	Comparisons	Combined Difference
<1	2	0.21 (-0.07, 0.48)	--	--
2*	--	--	9	0.40 (0.28, 0.52)
2	2	0.47 (0.21, 0.74)	5	0.32 (0.14, 0.50)
4*	7	0.35 (0.21, 0.49)	11	- 0.14 (-0.30, 0.02)
4	4	0.28 (0.14, 0.43)	5	0.03 (-0.11, 0.17)
6*	--	--	9	0.05 (-0.05, 0.15)
6	2	0.04 (-0.34, 0.44)	5	- 0.01 (-0.15, 0.13)
9*	--	--	5	- 0.07 (-0.19, 0.05)
9	2	0.18 (-0.01, 0.37)	3	- 0.11 (-0.27, 0.05)
12*	--	--	8	- 0.06 (-0.16, 0.04)
12	2	0.09 (-0.08, 0.26)	5	- 0.10 (-0.24, 0.04)

Note: Difference scores are relative to the group consuming a source of ω-3 LCPUFAs. * Includes non-randomized comparisons

Table 2 displays results of acuity measured with visual evoked potential (VEP). Preterm infants consuming formulas with ω-3 LCPUFAs were able to resolve finer patterns at 4-months-of-corrected age than their peers fed ω-3 LCPUFA-free formulas.

Table 2. Combined Estimates of Acuity Differences in Healthy Infants Measured With VEP

	Preterm Infants		Fullterm Infants	
Age Months	Comparisons	Combined Difference (95%CI)	Comparisons	Combined Difference
2*	--	--	6	0.24 (-0.05, 0.53)
2	--	--	4	0.28 (-0.07, 0.63)
4*	5	0.75 (0.51, 0.99)	10	0.26 (0.06, 0.46)
4	3	0.28 (0.44, 1.22)	5	0.15 (-0.09, 0.39)
6*	--	--	6	- 0.01 (-0.17, 0.15)
6	--	--	4	0.00 (-0.14, 0.14)
9*	--	--	3	- 0.12 (-0.24, 0.00)
9	--	--	2	- 0.12 (-0.28, 0.04)
12*	--	--	6	0.18 (-0.06, 0.42)
12	--	--	4	0.16 (-0.13, 0.45)

Note: See note for Table 1. VEP = visual evoked potential. A single comparison in fullterm infants showed better performance in w-3 LCPUFA group at 7-months-of-age. * Includes non-randomized comparisons.

DISCUSSION

Questions were presented on the possibility for conducting a meta-regression with levels of EFAs and LCPUFAs modeled as independent variables. It was subsequently suggested that the putative influence of nutrients from ω-3 and ω-6 should be considered simultaneously. A key issue to consider is that the reports contributing meaningful information to our analyses were not developed as dose-ranging studies; we felt that it was most appropriate for our modeling technique reflects this constraint. There is a practical issue to consider as well: data do not permit estimation of stable parameters with linear multivariable modeling techniques.

Another question was on the interpretation of our outcome variable. We report a relative difference score in octaves. A relative difference of 1 octave between groups indicates the average of the thinnest width of stimulus elements that people of one group are able to see is half that which people of the other group are able to see. Consider a square wave (see Figure) with equal width black stripes that repeat 2 times per cm (2 cycles/cm – each stripe is 0.25cm); if viewing distance is held constant (as it was in the infant acuity testing paradigms) a relative 1-octave change may be represented by a stimulus with black stripes of that repeat 4 times per cm. In this case, each black stripe would be 0.125cm wide and 50% thinner than the original stimulus. Continuing with this example, a 0.50 octave difference between the 2 cycle/cm stimulus would be represented by a stimulus with black stripes of that repeat 2.8 times per cm (this value represents a linear conversion from a 0.5 octave difference in the $\log_{10}$ scale: 0.75 $\log_{10}$ units, in this case). These stripes would be 0.179cm wide and project a retinal image that is approximately 30% thinner than the one produced by the 2 cy/cm stimulus.

We also briefly discussed the importance of using a systems-based approach to model critical periods in perceptual and cognitive development. I informed group members about John Colombo's recent work explaining how the 'transient' differences in acuity observed between dietary groups may operate in the development of vision-based cognitive processes.

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[i] For behaviorally-based tests, stimuli were square-wave gratings of two discrete luminances, presented in an equal duty cycle. These stimuli appear to adults as a series of vertical black and white stripes of equal width. For electrophysiologically-based tests stimuli were either square-wave gratings or checker-board patterns. A *cycle* is one period (that contains a single black and an adjacent white stripe). Researchers usually express grating acuity in units of *cycles per degree* (Cy/deg) of visual angle or log10 mean angle of resolution (log MAR). A *degree* is a unit of spatial extent which the physical stimulus projects on the retina. Cy/deg is a measure of visual resolving power per degree; higher acuity values represent response to finer patterns. To relate the measure to familiar metric -- when vision is corrected to a Snellen equivalent of 20/20, the observer has the ability to resolve 30 Cy/deg or logMAR 0.0 at 4m. All results obtained for this meta-analysis were converted to Cy/deg.